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Pharmaceutica Acta Helvetiae 74 (2000) 205–209

PHARMACEUTICA ACTA HELVETIAE

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Imidazoline receptors: a challenge

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Abstract

The hypotensive effect of imidazoline-like drugs (IMs) directly injected into the rostroventrolateral part of the brainstem (NRL/RVLM) was shown to involve non-adrenergic imidazoline specific receptors (IRs). Some IMs caused hypotension when injected there, irrespective of their affinity and selectivity for any α-adrenoceptor subtype. Compounds, such as LNP 509, S 23515, S 23757 or benazoline with very high selectivities for IRs over α_2-adrenoceptors (A_2Rs), became available recently. Some of these compounds (LNP 509, S 23515) caused hypotension when injected alone into the NRL/RVLM region. Nevertheless, high selectivity for IRs will not predict by its own the capability of IMs to elicit hypotension as some of these substances behaved as antagonists towards the hypotensive effects of the latter. As far as hybrid drugs, i.e., with mixed binding profiles (I_1/α_2), were concerned, a significant correlation has been reported between their central hypotensive effect and their affinity for IRs. Imidazoline antagonists, such as idazoxan, were repeatedly shown to competitively prevent and reverse the centrally induced hypotensive effect of IMs. The sole stimulation of A_2Rs within the NRL/RVLM region was not sufficient to decrease blood pressure as much as IMs did, as shown by the lack of significant blood pressure lowering effect of α-methylnoradrenaline (α-MNA). No correlation was observed between affinity of IMs for A_2Rs and their central hypotensive effects. It is also noticeable that yohimbine, an A_2Rs antagonist, was repeatedly shown to abolish the hypotensive effect of hybrids but usually in a non-competitive manner. Mutation of A_2Rs was shown to prevent the hypotensive effects of centrally acting drugs. It is concluded that (i) drugs highly selective for I_1Rs over A_2Rs can reduce blood pressure by their own; (ii) the central hypotensive effect of IMs needs implication of IRs and appears to be facilitated by additional activation of A_2Rs; and (iii) this effect requires intact A_2Rs along the sympathetic pathways.

Keywords: Imidazoline; Imidazoline receptors; Blood pressure; α_2-adrenoceptors

1. Introduction

It has been repeatedly reported that imidazoline compounds injected directly within the NRL/RVLM region, the site of the hypotensive action of clonidine-like drugs, reduced blood pressure whereas catecholamines did not (Bousquet et al., 1984; Ernsberger et al., 1987). Binding assays revealed the existence of imidazoline binding sites (IBS) (Ernsberger et al., 1987; Bricca et al., 1988) insensitive to catecholamines (Meeley et al., 1986; Bricca et al., 1994). Such binding sites were found in the brain as well as in peripheral tissues (Ernsberger et al., 1988; Wikberg, 1989; Molderings et al., 1991). Two sub-types of specific IBS were proposed. The I_1-subtype is sensitive to clonidine and idazoxan whereas the I_2-subtype, suggested being associated with the mitochondrial monoamine oxidase, is sensitive to idazoxan but poorly sensitive to clonidine (Bousquet et al., 1995; Molderings, 1997).

The only correlation ever reported in this domain was obtained by plotting affinities for IRs vs. blood pressure reductions of central origin (Ernsberger et al., 1990, 1997).

Such a correlation has never been shown when affinities for α_2-adrenoceptors were taken into account. There is a large body of evidence for the involvement of non-adrenoceptors in the induction of the hypotensive effect of imidazoline-related drugs (Bousquet, 1995, 1997; Ernsberger et al., 1997; Molderings, 1997). Nevertheless, one should keep in mind that the main side effects of clonidine-like drugs are clearly due to their capability of acti-

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0031-6865/00/$ - see front matter
PII: S0031-6865(99)00051-5

vating α_2-adrenoceptors. This particularly applies for sedation, which is due to activation of α_2-adrenoceptors located in the locus coeruleus (Bousquet, 1995; Bousquet et al., 1995).

Drugs with affinity for α_2-adrenoceptors lower than that of the leader compound clonidine and with high affinity for IRs are now available. Rilmenidine first and then moxonidine were proposed as drugs selective for IRs. Drugs selective for IRs over α_2-adrenoceptors were shown to cause marked hypotension from central origin; the incidence of their side effects is similar to that of placebos (Verbeuren et al., 1990).

A capacity of such drugs to target IRs is required to induce their hypotensive effects. Their residual affinity for α_2-adrenoceptors seems to play a synergistic role in their hypotensive action but is low enough to avoid the classical side-effects of the first generation of centrally acting antihypertensive drugs.

Questions related to the mechanism of the central hypotensive action induced by imidazoline-like drugs remain open. As an example, it is noteworthy that some pharmacological tools exhibiting high affinity for α_{2A}-adrenoceptors are capable of decreasing blood pressure by a central action. In fact, it was recently reported that, when α_2-adrenoceptors were made inactive, the hypotensive effects of compounds such as UK-14304 and dexmedetomidine were abolished (MacMillan et al., 1996). Thus, substances with high affinity for α_{2A}-adrenoceptors have actually the usual central effects of α_2-adrenoceptors agonists, i.e., hypotension, bradycardia, sedation, analgesic effects, mouth dryness and rebound effects.

2. Imidazoline specific binding sites

Ernsberger et al. used [^{3}H]*p*-aminoclonidine in membranes prepared from the bovine RVLM region and reported that 30% of the specific binding were insensitive to noradrenaline (Ernsberger et al., 1987). Similar results were obtained with [^{3}H]-idazoxan, another imidazoline, in renal cortical membranes (Coupry et al., 1987).

Catecholamine-insensitive specific IBS were described in numerous tissues including the human brain and kidney (Coupry et al., 1987; Langin and Lafontan, 1989; Parini et al., 1989). Bricca et al. (1988) reported that almost 80% of the specific binding of [^{3}H]-clonidine brainstem membranes were insensitive to noradrenaline. While I_2-IBS were clearly shown to be located on the external membrane of the mitochondria (Limon et al., 1992), I_1-IBS are present in synaptic plasma membranes (Heemskerk et al., 1998).

Several laboratories are currently tempting to purify specific IBS proteins. A 60-kDa protein with a pharmacological profile similar to that of the I_2-IBS was identified (Limon et al., 1992). The sequence of this protein proved some homologies with that of the monoamine oxidases. A 70-kDa protein, which also had pharmacological characteristics of the I_2-sites was purified from adrenal chromaffin cells (Wang et al., 1992).

Besides, a 43-kDa protein was purified from the human brain. This protein bound [^{3}H]-clonidine and [^{3}H]-idazoxan and was therefore considered to be an I_1-binding protein (Greney et al., 1994; Bennai et al., 1995). A similar protein (45 kDa) was also found in the rat brain (Escriba et al., 1994).

Coupling of IRs to G proteins is still debatable (Piletz and Sletten, 1993; Bricca et al., 1994). The signal transduction mechanism associated with the I_1-IRs is currently under investigation in several laboratories. Ernsberger et al. suggested recently that these receptors might be linked with a phosphatidylcholine selective phospholipase C (Separovic et al., 1996).

Specific IBS were labelled with tritiated *p*-aminoclonidine, clonidine, rilmenidine, idazoxan or *p*-iodoclonidine. These ligands are still largely employed in binding assays. However, they are not very selective for IRs as compared to α_2-adrenoceptors. Because of the relative lack of selectivity of the available radioligands and also because α_2-adrenoceptors and IRs usually appeared colocalized, it is still necessary to mask α_2-adrenoceptors in binding assays devoted to the characterization of IRs (Bricca et al., 1993, 1994). Radiolabelled ligands highly selective for IRs over α_2-adrenoceptors remain to be developed.

3. Selective ligands

3.1. Endogenous ligands

Several brain extracts have been shown to contain substances candidate(s) to be endogenous ligand(s) of these receptors (Atlas and Burstein, 1984a,b; Meeley et al., 1986; Ernsberger et al., 1988). Some of these extracts were shown hypotensive when applied centrally whereas others increased blood pressure when directly injected within the NRL/RVLM region (Meeley et al., 1986; Bousquet, 1995; Bousquet et al., 1986). The complete identification of the active substances contained in these extracts has not yet been achieved. Recently, agmatine, a decarboxylated metabolite of arginine, was proposed as an endogenous ligand of IRs. In fact, agmatine was capable of displacing in some extent the specific binding of various ligands from IRs (Li et al., 1994). Affinity of agmatine for IRs was rather low and it also bound to α_2-adrenoceptors and it had only weak blood pressure effects when applied within the NRL/RVLM area (Li et al., 1994; Sun et al., 1995; Regunathan and Reis, 1996). Until the identification of the specific endogenous ligand(s) of IRs would be achieved, it is impossible to state about the agonist or antagonist

properties of the synthetic substances that act on these receptors.

3.2. Synthetic ligands

Recently, benazoline, an imidazoline about 10,000 times more selective for IRs than for α_2-adrenoceptors has become available (Brasili et al., 1996). When administered intracisternally (i.c.) to pentobarbital anaesthetized rabbits, benazoline (3 μmol/kg) tended to increase mean arterial pressure. This surprising effect was much more pronounced in animals with muscimol induced sympathetic inhibition (MAP raised by 150%).

We were also particularly interested in an imidazoline derivative with selectivity for imidazoline receptors over α_2-adrenoceptors of 1000 to 10,000, according to binding data. This substance, called LNP509, was synthesized in our laboratory. When administered directly in the central nervous system by the intracisternal route in anaesthetized rabbits, it decreased blood pressure in a dose-dependent manner (100 to 1000 μg/kg) (Bousquet et al., 1999).

S23515 also exhibited high affinity for I_1Rs and its selectivity ratio (I_1 over A_2Rs) was over 4000. When administered i.c. in cumulative doses (10–300 μg/kg) in anaesthetised rabbits, S23515 induced a dose-dependent decrease in blood pressure and heart rate.

From the data obtained with LNP509 and S23515 compounds, one can conclude that a very selective action on medullary specific imidazoline receptors alone was sufficient to trigger hypotension. However, it remains to be clarified whether the hypotensive compounds are agonists for IRs and benazoline an inverse agonist or vice versa. Idazoxan and efaroxan, which have no effect by themselves on blood pressure when delivered the same ways at reasonable doses, remain pure antagonists.

A possible interaction between I_1Rs and A_2Rs was also investigated. α-Methylnoradrenaline (α-MNA), a selective A_2Rs agonist with no affinity at all for IRs, and S23515 were injected (i.c.) in combination. Doses of these compounds, too low to modify blood pressure when given alone, were selected (0.5 and 3 μg/kg, respectively). S23515 was injected 10 min before α-MNA. Combination of both drugs caused a significant hypotensive effect (−23 ± 2%). Very similar results were obtained with LNP509 compound in combination with α-MNA.

Taken together, all these results provide the first evidence that (i) a drug highly selective for I_1Rs over A_2Rs can reduce blood pressure and (ii) actions on I_1Rs and A_2Rs may potentiate each other, suggesting an interaction between these two types of receptors. Such an interaction may account for the overall hypotensive effect of *hybrid* drugs such as clonidine, which bind to both I_1Rs and A_2Rs. Whether there is a direct link between these two types of receptors on the same neuron or whether they are operating in series along the sympathetic pathways as suggested by Head (1995) remains to be demonstrated.

3.3. The second generation of central hypotensive drugs

Rilmenidine, an imidazoline-like oxazoline, was presented as the first centrally acting antihypertensive drug selective for IRs (Verbeuren et al., 1990; Head et al., 1993). Thus, this substance was the prototype of such drugs. Its hypotensive effect mostly originates within the brain (Feldman et al., 1990; Ernsberger et al., 1997). Due to its reduced affinity for α_2-adrenoceptors as compared to clonidine, rilmenidine was shown to be selective for IRs (Bricca et al., 1989). This selectivity of rilmenidine for IRs over α_2-adrenoceptors might explain that at hypotensive doses it is devoid of any significant sedative action in animal models as well as in patients. Idazoxan, an antagonist with an imidazoline structure, was much more active than yohimbine, a reference antagonist of the α_2-adrenoceptors, to prevent the hypotensive effect of rilmenidine (Feldman et al., 1990). All these experimental observations confirmed that IRs are mainly involved in the blood pressure lowering effect of rilmenidine.

In addition, to its hypotensive effect, rilmenidine has additional beneficial effects. In the cardiovascular field, it was shown to powerfully prevent the occurrence of experimental ventricular arrhythmias. Mammoto et al. (1996) reported that rilmenidine prevented the halothane-adrenaline induced arrhythmias in dogs. Our group has shown that rilmenidine was able to prevent the occurrence of ventricular arrhythmias caused by bicuculline injected i.c. in anaesthetized rabbits. This effect of potential clinical relevance was observed when rilmenidine was injected either i.c. or intravenously (Roegel et al., 1996). It is notable that this anti-arrhythmic action was observed at doses of rilmenidine too low to reduce blood pressure and that it was antagonized by idazoxan. Similar results were also obtained with moxonidine (Lepran and Papp, 1994; Mest et al., 1995).

4. Conclusion

In conclusion, as far as the respective contributions of α_2-adrenoceptors and imidazoline receptors in the hypotensive effect of clonidine-like drugs are concerned, the state of the art can be summarized as follows.

(1) Non-adrenergic receptors specific for imidazoline-like compounds do exist and are physically different from the classical α_2-adrenoceptors.

(2) An action on medullary imidazoline receptors alone is sufficient to inhibit the vasomotor tone and therefore to reduce blood pressure. Actually, the same holds true for the exclusive stimulation of α_2-adrenoceptors within the central nervous system.

(3) Imidazoline specific receptors are involved in the hypotensive effects of imidazoline selective compounds as well as of clonidine-like (hybrid) drugs.

(4) The integrity of the α_2-adrenoceptors included in the sympathetic centers and pathways appears to be re-

quired for the development of the hypotensive effects of at least α_2-adrenergic agonists and hybrid drugs.

(5) A cooperative interaction between imidazoline receptors and α_2-adrenoceptors seems to account for the marked and rapid hypotensive effect caused by hybrid drugs, such as clonidine.

Acknowledgements

We gratefully acknowledge Prs Pigini, Giannella and Brasili, Camerino and Modena Universities for generously providing benazoline and SERVIER laboratories for providing compound S23515.

References

Atlas, D., Burstein, Y., 1984a. Isolation of an endogenous clonidine-displacing substance from rat brain. FEBS Lett. 170, 387–390.

Atlas, D., Burstein, Y., 1984b. Isolation and partial purification of a clonidine displacing endogenous brain substance. Eur. J. Biochem. 144, 287–293.

Bennai, F., Greney, H., Stutzmann, J., Bousquet, P., Dontenwill, M., 1995. Development of anti-idiotypic antibodies specific for the human cerebral imidazoline receptor. Ann. N. Y. Acad. Sci. 763, 140–148.

Bousquet, P., 1995. Recent advances in imidazoline receptor research. Exp. Opin. Invest. Drugs 4 (5), 431–442.

Bousquet, P., 1997. Imidazoline receptors. Neurochem. Int. 30, 3–7.

Bousquet, P., Feldman, J., Schwartz, J., 1984. Central cardiovascular effects of α-adrenergic drugs: difference between catecholamines and imidazolines. J. Pharmacol. Exp. Ther. 230, 230–236.

Bousquet, P., Feldman, J., Atlas, D., 1986. An endogenous, non-catecholamine clonidine antagonist increases mean arterial blood pressure. Eur. J. Pharmacol. 124, 167–170.

Bousquet, P., Greney, H., Bennai, F., Feldman, J., Stutzmann, J., Belcourt, A., Dontenwill, M., 1995. Imidazoline receptors and cardiovascular regulations: a statement. Ann. N. Y. Acad. Sci. 763, 526–530.

Bousquet, P., Bruban, V., Schann, S., Greney, H., Ehrhardt, J.D., Dontenwill, M., Feldman, J., 1999. Participation of imidazoline receptors and α_2-adrenoceptors in the central hypotensive effects of imidazoline-like drugs. Ann. N. Y. Acad. Sci. 881, 272–278.

Brasili, L., Pigini, M., Bousquet, P., Carotti, A., Dontenwill, M., Giannella, M., Moriconi, R., Piergentili, A., Quaglia, W., Tayebati, S.K., 1996. Discovery of highly selective imidazoline receptor ligands. Perspective in Receptor Research 24, 361–376.

Bricca, G., Dontenwill, M., Molines, A., Feldman, J., Belcourt, A., Bousquet, P., 1988. Evidence for the existence of a homogenous population of imidazoline receptors in the human brainstem. Eur. J. Pharmacol. 150, 401–402.

Bricca, G., Dontenwill, M., Molines, A., Feldman, J., Tibiriça, E., Belcourt, A., Bousquet, P., 1989. Rilmenidine selectivity for imidazoline receptors in human brain. Eur. J. Pharmacol. 163, 373–377.

Bricca, G., Greney, H., Dontenwill-Kieffer, M., Zhang, J., Belcourt, A., Bousquet, P., 1993. Heterogeneity of the specific imidazoline binding of [^{3}H]idazoxan in the human cerebral cortex. J. Neurochem. Int. 2, 153–163.

Bricca, G., Greney, H., Zhang, J., Dontenwill, M., Stutzmann, J., Belcourt, A., Bousquet, P., 1994. Human brain imidazoline receptors: further characterisation with [^{3}H]clonidine. Eur. J. Pharmacol., Mol. Pharmacol. Sect. 266, 25–33.

Coupry, I., Podevin, R.A., Dausse, J.P., Parini, A., 1987. Evidence for imidazoline binding sites in basolateral membranes from rabbit kidney. Biochem. Biophys. Res. Commun. 147, 1055–1060.

Ernsberger, P.R., Meeley, M.P., Mann, J.J., Reis, D.J., 1987. Clonidine binds to imidazoline binding sites as well as α_2-adrenoceptors in the ventrolateral medulla. Eur. J. Pharmacol. 134, 113.

Ernsberger, P.R., Meeley, M.P., Reis, D.J., 1988. An endogenous substance with clonidine like properties: selective binding to imidazole sites in the ventrolateral medulla. Brain Res. 441, 309–318.

Ernsberger, P., Giuliano, R., Willette, R.N., Reis, D.J., 1990. Role of imidazole receptors in the vasodepressor response to clonidine analogs in the rostro-ventrolateral medulla. J. Pharmacol. Exp. Ther. 253, 408–418.

Ernsberger, P., Friedman, J.E., Koletsky, R.J., 1997. The I_1-imidazoline receptor: from binding site to therapeutic target in cardiovascular disease. J. Hypertens. 15 (suppl), S9–S23.

Escriba, P.V., Sastre, M., Wang, H., Regunathan, S., Reis, D.J., Garcia-Sevilla, J.A., 1994. Immunodetection of putative imidazoline receptor proteins in the human and rat brain and other tissues. Neurosci. Lett. 178, 81–84.

Feldman, J., Tibiriça, E., Bricca, G., Dontenwill, M., Belcourt, A., Bousquet, P., 1990. Evidence for the involvement of imidazoline receptors in the central hypotensive effect of rilmenidine in the rabbit. Br. J. Pharmacol. 100, 600–604.

Greney, H., Bennai, F., Molines, A., Belcourt, A., Dontenwill, M., Bousquet, P., 1994. Isolation of a human cerebral imidazoline-specific binding protein. Eur. J. Pharmacol. 265, R1–R2.

Head, G.A., 1995. Importance of imidazoline receptors in the cardiovascular actions of centrally acting antihypertensive agents. Ann. N. Y. Acad. Sci. 763, 531–540.

Head, G.A., Godwin, S.J., Sannajust, F., 1993. Differential receptors involved in the cardiovascular effects of clonidine and rilmenidine in conscious rabbits. J. Hypertens. 11 (5), S322–S325, Suppl.

Heemskerk, F.M.J., Dontenwill, M., Greney, H., Vonthron, C., Bousquet, P., 1998. Evidence for the existence of imidazoline specific binding sites in synaptosomal plasma membranes of the bovine brainstem. J. Neurochem. 71, 2193–2202.

Langin, D., Lafontan, M., 1989. [^{3}H]-idazoxan binding at non-α_2-adrenoceptors in rabbit adipocyte membranes. Eur. J. Pharmacol. 159, 199–203.

Lepran, I., Papp, J.P., 1994. Effect of moxonidine on arrhythmias induced by coronary artery occlusion and reperfusion. J. Cardiovasc. Pharmacol. 24 (1), S9–S15, Suppl.

Li, G., Regunathan, S., Barrow, C.J., Eshraghi, J., Cooper, R., Reis, D.J., 1994. Agmatine: an endogenous clonidine displacing substance in the brain. Science 263, 966–969.

Limon, I., Coupry, I., Lanier, S.M., Parini, A., 1992. Purification and characterisation of mitochondrial imidazoline-guanidinium receptive site from rabbit kidney. J. Biol. Chem. 267, 21645–21649.

MacMillan, L.B., Hein, L., Smith, M.S., Piascik, M.T., Limbird, L.E., 1996. Central hypotensive effects of the α_{2A}-adrenergic receptor subtype. Science 273, 801–803.

Mammoto, T., Kamabayashi, T., Hayashi, Y., Yamatodani, A., Takada, K., Yoshiya, I., 1996. Antiarrhythmic of rilmenidine on adrenaline-induced arrhythmia via central imidazoline receptors in halothane anaesthetized dogs. Br. J. Pharmacol. 117, 1744–1748.

Meeley, M.P., Ernsberger, P.R., Granata, A.R., Reis, D.J., 1986. An endogenous clonidine-displacing substance from bovine brain: receptor binding and hypotensive actions in the ventrolateral medulla. Life Sci. 38, 1119–1126.

Mest, H.J., Thomsen, P., Raap, A., 1995. Antiarrhythmic effect of the selective I_1-imidazoline receptor modulator moxonidine on ouabain-induced cardiac arrhythmia in guinea pigs. Ann. N. Y. Acad. Sci. 763, 620–633.

Molderings, G.J., Hentrich, F., Göthert, M., 1991. Pharmacological characterisation of the imidazoline receptor which mediates inhibition of noradrenaline release in the rabbit pulmonary artery. Naunyn-Schmiedberg's Arch. Pharmacol. 344, 630–638.

Molderings, G.J., 1997. Imidazoline receptors: basic knowledge, recent advances and future prospects for therapy and diagnostic. Drug of the Future 22 (7), 757–772.

Parini, A., Coupry, I., Graham, R.M., Uzielli, I., Atlas, D., Lanier, S.M., 1989. Characterisation of an imidazoline/guanidinium receptive site distinct form the α_2-adrenergic receptor. J. Biol. Chem. 264, 11874–11878.

Piletz, J.E., Sletten, K., 1993. Nonadrenergic imidazoline binding sites on human platelets. J. Pharmacol. Exp. Ther. 267, 1493–1502.

Regunathan, S., Reis, D.J., 1996. Imidazoline receptors and their endogenous ligands. Annu. Rev. Pharmacol. Toxicol. 36, 511–544.

Roegel, J.C., Yannoulis, N., De Jong, W., Monassier, L., Feldman, J., Bousquet, P., 1996. Inhibition of centrally-induced ventricular arrhythmias by rilmenidine and idazoxan in rabbits. Naunyn-Schmiedeberg's Arch. Pharmacol. 354, 598–605.

Separovic, D., Kester, M., Ernsberger, P., 1996. Coupling of I_1-imidazoline receptors to diacylglyceride accumulation in PC12 rat pheochromocytoma cells. Mol. Pharmacol. 49, 668–675.

Sun, M.K., Regunathan, S., Reis, D.J., 1995. Cardiovascular responses to agmatine, a clonidine displacing substance, in anaesthetized rats. Clin. Exp. Hypertens. 17, 115–128.

Verbeuren, T.J., Dinh Xuan, A.T., Koenig-Bérard, E., Vitou, P., 1990. Rilmenidine. Cardiovasc. Drug Rev. 8, 56–70.

Wang, H., Regunathan, S., Meeley, M.P., Reis, D.J., 1992. Isolation and characterisation of imidazoline receptor protein from bovine adrenal chromaffin cells. Mol. Pharmacol. 42, 792–801.

Wikberg, J.E.S., 1989. High affinity binding of idazoxan to a non-catecholaminergic binding site in the central nervous system: description of a putative idazoxan-receptor. Pharmacology and Toxicology 64, 152–155.